Advances in Molecular and Cellular Microbiology 4

Susceptibility to Infectious Diseases

The Importance of Host Genetics

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CAMBRIDGE
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS
The Edinburgh Building, Cambridge CB2 2RU, UK
40 West 20th Street, New York, NY 10011-4211, USA
477 Williamstown Road, Port Melbourne, VIC 3207, Australia
Ruiz de Alarcón 13, 28014 Madrid, Spain
Dock House, The Waterfront, Cape Town 8001, South Africa

http://www.cambridge.org

First published 2004

Printed in the United States of America

Typefaces FF Scala 9.5/13 pt., Formata and Quadraat Sans *System* LaTeX 2_ε [TB]

A catalog record for this book is available from the British Library.

Library of Congress Cataloging in Publication Data

Susceptibility to infectious diseases : the importance of host genetics / edited by Richard Bellamy.

p. ; cm. – (Advances in molecular and cellular microbiology)

Includes bibliographical references and index.

ISBN 0-521-81525-8 (hardback)

1. Disease susceptibility. 2. Infection. 3. Host-parasite relationships – Genetic aspects. 4. Medical genetics. I. Bellamy, Richard (Richard John) II. Series.

[DNLM: 1. Communicable Diseases – genetics. 2. Communicable Diseases – immunology. 3. Genetic Predisposition to Disease. 4. Immunologic Deficiency Syndromes – genetics. WC 100 S964 2004]

RB153 .S875 2004
616.9′0442 – dc21 2003046270

ISBN 0 521 81525 8 hardback

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CHAPTER 1

Introduction

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Patients suffering from a serious illness frequently ask "Why did this happen to me?" When the disease is cancer or cardiovascular disease, patients recognise the risk of inheriting "bad genes" from parents as readily as the risks from smoking and diet. It is all too clear that if both our parents suffered myocardial infarcts at an early age we must be at increased risk of the same thing happening to ourselves. However, when asked why someone developed a serious infection, we generally blame lack of acquired immunity, environmental factors, or bad luck. Increasingly it appears that "bad luck" really means the genes we have inherited.

It is a common misapprehension that our genes are not important in determining our ability to fight off infectious diseases. In fact a study of almost 1,000 adoptees in Denmark found that the host genetic component of susceptibility to premature death from infection is greater than for cancer and cardiovascular disease (Sorensen et al., 1988). This is not unexpected as common diseases which cause high mortality exert the greatest evolutionary effects on the human genome. Prior to this century infectious diseases were the major cause of death in the western world and still are in many developing countries. From this we can surmise that microorganisms have been the major selective force in recent human evolution. In other words the interaction between the genes of our ancestors and those of human pathogens have resulted in what makes each of us genetically unique today.

When a population is exposed to an environmental factor for many generations, evolution results in adaptation to it. This is most apparent in the differences in skin and eye colour which occur between populations exposed to different amounts of sunlight. Similarly, the longer a population has been exposed to an infectious disease, the more resistant we should expect the current members of that population to be to it. After several generations of

exposure the more genetically susceptible individuals are killed off and the frequency of disease-resistance genes in the population increases. This can most clearly be seen for malaria because it is restricted to certain geographic regions and exerts high mortality. Comparisons of gene frequencies in different populations have enabled the identification of several genetic variants conferring malaria resistance, including sickle cell haemoglobin, glucose-6-phosphate dehydrogenase deficiency, α-thalassaemia and the Duffy-negative erythrocyte phenotype. Conversely, when a population is first exposed to an infectious disease, we should expect them to be highly susceptible to it. This was strikingly observed when the population of the Qu'Appelle Indian Reservation, Saskatchewan, first came into contact with tuberculosis in the 1890s. Initially the annual tuberculosis-related death rate was almost 10% of the population. After 40 years, when two generations had passed, more than half of the families were eliminated and the annual tuberculosis death rate had fallen to only 0.2%. This fall in mortality rate is believed to be because of "weaning out" of tuberculosis-susceptibility genetic factors (Motulsky, 1960). Massive death rates from measles, smallpox, and other infections, which occurred when the conquistadors first visited the Americas, are also likely to have been due to a combination of genetic susceptibility and lack of acquired immunity.

The following chapter, by Alcaïs and Abel, provides an overview of the approaches which can be used to identify the host genes involved in susceptibility to infectious diseases. It is clear that no single method could be used to identify all of these genes. A wide range of methods must be used to dissect out the complex genetic factors underlying the multifactorial aetiology of susceptibility to specific pathogens. The task is not easy and the results of different studies have sometimes been contradictory. However, the subsequent chapters of the book show that difficulties have been overcome and substantial progress has already been made in understanding genetic susceptibility to many different pathogens. A wide range of approaches has been used, including population linkage and association studies, extrapolations from mouse-models of disease, and *in vitro* studies of immune function. Each chapter illustrates a different scientific approach providing insight into the uses and limitations of each method.

In Chapter 3, Vihinen provides a summary of the large number of rare, monogenic immunodeficiency syndromes which have now been identified. In many cases the molecular basis underlying the condition has been identified and catalogues and databases now provide ready access to the current state of knowledge. Yee and Thursz, in Chapter 4, describe the extreme polymorphism of the major histocompatibility complex and how this has evolved

in response to pressure from microorganisms. The present significance of this variability is shown by examples of how possessing particular human leukocyte antigen genotypes may increase our risk of developing serious complications following exposure to specific pathogens. Children with cystic fibrosis are more susceptible to infections with bacteria such as *Pseudomonas aeruginosa* and *Burkholderia cepacia*. In Chapter 5, Cuthbert discusses the molecular basis underlying cystic fibrosis and why it results in susceptibility to specific microorganisms. He also discusses the intriguing possibility that the common gene mutations causing cystic fibrosis have been selected for by conferring heterozygote resistance to other pathogens.

The greatest advances in our understanding of susceptibility to any single infectious disease have been with malaria. In Chapter 6, Roberts discusses how the geographical restriction of this disease and its high mortality have resulted in marked variability in the frequency of common variants in the haemoglobin and other genes. Human immunodeficiency virus (HIV) is a very new disease compared to malaria and has not yet had sufficient time to exert a major influence on the evolution of the human genome. However the recognition that some persons who had been repeatedly exposed to HIV had never become infected led to the suspicion that these subjects may have innate immunity to the condition. In Chapter 7, Tang and Kaslow describe how studies on such subjects determined that their macrophages could not be infected by HIV and led to the discovery that they lacked expression of the membrane protein, chemokine receptor 5, due to a 32-basepair deletion in this gene. In contrast, the discovery of the *Nramp1* gene was made by studying a mouse model of susceptibility to mycobacteria and other intracellular pathogens. Gros and Schurr, in Chapter 8, describe the long process of identifying this murine gene by positional cloning and the subsequent studies to ascertain its function. Large population studies have since been performed confirming that the human homologue of this gene is important in human susceptibility to tuberculosis. In Chapter 9, Casanova describes how a very different approach was used to identify how five genes in the interferon-γ signalling pathway are involved in human susceptibility to mycobacterial infections. Investigation of children who suffered from recurrent infections with atypical mycobacteria, or who developed disseminated infections following vaccination with bacille Calmette-Guerin, led to these discoveries.

Mannose binding lectin (MBL) deficiency is discussed by Jack, Klein, and Turner in Chapter 10. This defect of opsonisation was first described in a child with recurrent bacterial infections in 1968. Since then many infectious diseases have been found to be associated with MBL deficiency. The three principal gene mutations causing MBL deficiency have been found at very

high frequency in most populations studied. Whether these gene variants have been selected for by conferring resistance to an intracellular pathogen is still uncertain. Polymorphism in blood groups and secretor status may also have evolved due to exposure to an infectious disease. A large number of studies have found associations between infectious diseases and blood group phenotypes and/or secretor status. In Chapter 11, Blackwell and colleagues discuss how blood group antigens may act as receptors for microorganisms, facilitating mucosal colonisation, and tissue invasion.

In Chapter 12, Dessein et al. describe how they identified that two different genes influence immunity to *Schistosoma mansoni* and subsequent development of liver disease. A gene in the cytokine cluster on chromosome 5q31–33 influences worm burden and a gene on chromosome 6q21–23, in the region of the interferon-γ receptor 1 gene, determines who will develop periportal fibrosis. In the final chapter Bishop and Ironside discuss prion diseases. The interactions between the host genotype and the different prion proteins offer valuable insight into the nature of these diseases. This has proved valuable in developing models of the likely future epidemic curve for new variant Creutzfeldt–Jakob disease.

This is an exciting time to be studying the role of genetic factors in multifactorial diseases. With the success of the human genome project and advances in molecular biology and bioinformatics, significant advances in our understanding of complex diseases should be forthcoming. For many infectious diseases it is clear that interaction between many host genes and environmental factors will be involved in determining the outcome of infection. The greater the number of genes involved, the more difficult it will be to predict who will develop a particular infection and who will die from it. For example, it is uncertain if it will ever be possible to predict exactly who will develop new variant Creutzfeldt–Jakob disease, tuberculosis, or cerebral malaria and who will not. However, identifying host disease-susceptibility genes will provide valuable insight into disease pathogenesis.

The chapters in this book discuss how the advances, which have been made in host genetics, may eventually find applications in the development of novel therapeutic and preventative strategies. Identification of MHC associations with disease may lead to development of vaccines, the cystic fibrosis transmembrane regulator may eventually be replaced by gene therapy, chemokine receptor blockers may be used in the treatment of HIV, mannose binding lectin replacement may become available, and antiadhesion therapy may be used to stop pathogens binding to host cell receptors. For those working in this field there is still much work to be done. In this era of emerging infections and antibiotic-resistant bacteria, physicians need every possible

weapon to combat human pathogens. Advancing our understanding of the interaction between host and pathogen genomes should hopefully provide some new weapons to add to our arsenal.

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